THE LESIONS IN EXPERIMENTAL INFECTION WITH BACTERIUM TULARENSE*

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In 1911 McCoy[1] discovered a disease among the ground squirrels of California the lesions of which resembled somewhat closely, at least in the gross features, those produced in rodents by Bacillus pestis. In 1912, with Chapin, McCoy[2] reported the isolation of the microbic cause of these lesions, and to the organism he gave the name Bacterium tularense. This organism was exceedingly pathogenic for rodents and for monkeys, an observation which led McCoy to suggest in a letter to Wherry[3] that it might be expected sooner or later to be encountered in human infections. This prophecy materialized: in 1914 Wherry and Lamb[4] reported finding B. tularense in a case which they had been investigating for Dr. Vail,[5] under the suspicion that it might be glanders.

This first patient was a meat cutter in a restaurant. At the time of examination he was suffering from an acute ulcerative conjunctivitis, enlarged cervical lymph glands, fever, and prostration. Later, a second case was sent them by Dr. Sattler,[6] in which the lesions and symptoms were identical with those observed in the first case.

With the organism isolated from these cases, Wherry and Lamb made a considerable number of inoculations of laboratory animals, the organs of which were referred to the writer for study. In each instance practically the same lesions were found, and variations, when they occurred, were chiefly ones of size. The gross lesions have been described by Wherry and Lamb.[4]

The following are descriptions of the typical lesions as they appeared in the different organs.

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1. Bull. Hyg. Lab., U. S. P. H. and M.-H. S., 1911, 43.
2. Ibid., 1912, 53.
3. U. S. Pub. Health Rep., 1914, *29*, p. 3387.
4. Jour. Infect. Dis., 1914, 15, p. 331. Jour. Am. Med. Assn., 1914, 63, p. 2041.
5. Ophth. Rec., 1914, 23, p. 487. Jour. Mich. Med. Soc., 1915, 14, p. 3.
6. Arch. Ophth., 1915, 44, p. 265.

Tissues were fixed in alcohol or Zenker's solution and imbedded in paraffin. They were stained by Gram's method, with hematoxylin and eosin, eosin and methylene blue, carbolthionin, and Borrel's stain.

In the skin, the lesions were somewhat diffusely necrotic in type, and in them, altho there were numerous polymorphonuclear leukocytes, the appearances indicated that tissue necrosis was the primary lesion and that this was followed by invasion of leukocytes. The picture was that of a not sharply circumscribed, rapid, necrotic process which involved all layers of the skin and subcutaneous tissue. The subjacent muscle was affected to a less extent. There were evidences in the necrotic areas of focalization of the process in the immediate neighborhood of blood vessels. In these foci, there were fewer leukocytes, often none, and only the detritus of destroyed cells with scattered masses of nuclear fragments. This is the kind of lesion encountered in the abdominal wall after puncture or scarification, and is of the same type which follows infection of the conjunctiva.

The lymph glands were swollen very evidently and were the seats of exquisite sinus catarrhus and edema. Besides this generalized lymphadenoid process there were foci of focal necrosis, which were sometimes large but usually small, and located for the most part in the germinal centers. In some instances the necrosis was more extensive; in such the acute catarrhal condition was less vivid and the necrosis involved more or less the whole gland as well as the surrounding tissues. Here again, altho there was some neighboring polynucleosis, necrosis with extreme karyorrhexis dominated the picture.

The spleens exhibited practically the same lesions as the lymph glands, i. e., very numerous areas of focal necrosis, some very minute, others relatively large, many confluent. In the very small ones there was evidence of nothing but the death and rhexis of a few cells, about which there was no apparent cellular reaction, unless occasionally the surrounding cells appeared somewhat paler than those more distant from the lesions. In the larger lesions there was frequently a reaction evident about the necrotic areas, which was characterized by only moderate numbers of polymorphonuclear leukocytes. The follicles, when they were not involved in the necrosis, were generally hyperplastic, and the pulp was exceedingly congested. Occasionally whole follicles were necrotic. In no place were giant cells observed.

The liver sections, as a rule, showed more, but also, as a rule, smaller, lesions than the spleen. Here and there throughout the tissue one could see very small palely staining areas composed of but few cells which often showed nothing but the lack of stain. Also scattered about were larger areas in which the cells stained only a pale pink with little or no evidence of nuclei. In other foci the nuclei were undergoing fragmentation; and in still other and larger ones the fragmentation was extreme, the cytoplasm was less stainable, and there was a slight polymorphonuclear reaction about the areas. Removal of the débris produced in the lesions is apparently accomplished by means of polymorphonuclear phagocytes. There was no evidence of autolysis and none of participation by endothelial leukocytes.

The hepatic lesions showed no definite predilection for a particular part of the lobule, but occurred more or less indiscriminately scattered. Very small areas of capillary hemorrhage suggested, what would be supposed, that the organism reaches the organ by way of the blood stream; and yet the lesions did not predominate in the central or capillary zone of the lobules. Sometimes they appeared directly in or upon the wall of a fairly large-sized vessel, sometimes apparently in connection with the interlobular bile ducts. In one

small lesion a stellate figure, such as has been described by Wolbach,[7] appeared. In no section could any organism be distinctly stained by any method used.

In sections from the lungs, there were areas of lobular pneumonia and diffuse inflammatory edema. The pneumonic process was, as a rule, an acute hemorrhagic one, and the alveoli were filled with erythrocytes, desquamated alveolar epithelium, and lymphocytes. There were occasional polymorphonuclear leukocytes, but these were scant as compared with the numbers encountered in the ordinary pneumonias. In the large blood vessels, however, there were increased numbers of polymorphonuclear leukocytes; in the tissues they appeared in number only about the areas of necrosis. The earliest lesions indicated that the areas of consolidation and necrosis had arisen in much the same way as those in the other organs; namely, as areas of focal death resulting from the toxic agent brought by the blood stream. Probably the bacterium had been fixed by the endothelium of a capillary, and had then reproduced, caused a necrosis of the tissue, and produced an inflammatory edema involving the neighboring alveoli, and more necrosis. At a safe distance about the lesions, the polymorphonuclears had attempted to form a protective zone. The first impression which one had from certain sections was that one was dealing with an acute caseous pneumonia. No acid-fast or other organism could be found, however.

In sections from the intestinal tract, there were no striking lesions; nothing, for instance, which approximated those seen in the regional lymph glands draining the point of superficial infection. The lymphoid follicles were moderately enlarged. They showed no evidence of necrosis and no increased number of polymorphonuclears. Upon the mucous membrane, which was moderately congested, there was a slight catarrhal exudate and nothing more.

The kidney sections showed extreme edema and cloudy swelling, almost an acute necrosis. There were no areas of necrosis and no areas of cellular infiltration.

There were no obvious changes in the central nervous system, in the heart, or in the adrenals, tho the latter organs were congested.

According to Ledingham,[8] the lesions of spontaneous rat plague in the spleen are necrotic in type, with or without polymorphonuclear leukocytes. Associated with these lesions, there are pulp hemorrhages. The liver lesions are karyorrhectic. In the lymph glands there are no capsule changes. There are karyorrhexis of lymphoid cells and a very large amount of nuclear detritus lying free or included in large endothelioid phagocytic cells. There are many large cells of endothelioid type throughout the nodes and many of these show mitotic figures. The lesions, therefore, are essentially focal necroses to start with, which may become abscesses, or which may show merely karyorrhexis with endothelial stimulation and proliferation. In tularense infections, the lesions are essentially areas of necrosis with, in no case, suppuration, except in the case of the skin. There is no evidence in any section of any marked proliferation on the part of the endothe-

8. Jour. Hyg., 1907, 3, p. 359.
7. Jour. Med. Research, 1911, 24, p. 243.

lial cells, as is true in plague and typhoid. In the smallest lesion in the liver, where the process is limited and clearest, the earliest change seems to be degeneration of the liver and endothelial cells with very early karyorrhexis. In this stage there are a few lymphocytes present but no polymorphonuclear leukocytes. The latter move to the region of the lesions following the degeneration of the cells and never occur within the lesions in large numbers as in plague. Were there more endothelial proliferation, the lesions might resemble those of typhoid.